

VALPROATE-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY: A CASE REPORT

Dear Editor:

Valproic acid (VPA) is an antiepileptic drug that is approved for the treatment of several types of seizures. It is also prescribed for the treatment of bipolar disorder, schizoaffective disorder, social phobias, neuropathic pain, and for the prophylaxis and treatment of migraine headaches.¹ VPA and its derivatives have been found to be useful and generally safe in the treatment of bipolar disorder, agitation in dementia, and refractory anxiety disorders in the elderly.²⁻⁴ These drugs are known to cause hyperammonemia and associated encephalopathy, but most of these data come from studies of children and young adults.⁵⁻¹⁰ We report a case of an adolescent who suffered idiopathic generalized epilepsy and presented with subacute cognitive impairment and worsening of seizures a few months after starting treatment with VPA. No biochemical signs of overdose or toxicity were observed. Withdrawing VPA resulted in a swift improvement in the patient's mental status.

Case Report. Our patient was a 17-year-old adolescent boy with known diagnoses of autistic disorder and epilepsy. He presented to hospital with aggressive behaviour toward self and others. He had started taking VPA (1500mg/d) five months previously for the treatment of epilepsy. The patient had no history of developmental delay or metabolic defects. He denied having any fever, headaches, or other symptoms of neurologic or liver disease. On examination the next day after admission, the patient was drowsy but responsive, and he answered questions appropriately. His vital signs were stable and the results

of a neurologic examination were otherwise unremarkable. The patient had asterixis, but no signs of jaundice and no stigmata of chronic liver disease. The findings of the remainder of the physical examination were normal. Results of initial investigations, including a complete blood count and tests for electrolytes, creatinine, and liver biochemistry were normal. The results of a toxicology screen were unremarkable. The patient's serum valproate level was 81. In the first 48 hours after admission, his level of consciousness fluctuated. The patient had a grand mal seizure when he woke up in the morning of the next day. He was unresponsive after the seizure. The emergency medical service was called and he was taken by life squad to the emergency room (ER) and examined by the neurologist and attending ER resident. He was still drowsy but he was oriented to place and person. Subsequent tests revealed an elevated venous ammonia level. He was kept in the ER for a day and then he was transferred to Neurology floor for further care. On follow up metabolic panel, his liver biochemistry was normal; thus, valproate-related hyperammonemic encephalopathy was suspected. Valproate dose was immediately decreased, and over the next week, the patient's level of consciousness improved along with decline in the ammonia level.

Discussion. Encephalopathy and elevated levels of serum ammonia is often attributed to liver failure. However, other conditions, including valproate-related hyperammonemic encephalopathy, must be considered. Unfortunately, few physicians are aware of this rare condition. In our case, the clues to the correct diagnosis were the patient's normal hepatic function, history of valproate use, and improvement in clinical condition and eventual resolution after a reduction in dose of VPA. Although the exact

incidence of valproate-related hyperammonemic encephalopathy is not known, mild and reversible elevations in ammonia have been described in 16 to 52 percent of patients receiving valproate therapy.¹² In a case series, asymptomatic hyperammonemia was observed in 52 percent of patients receiving valproate monotherapy.¹² Although its pathogenesis is not completely understood, hyperammonemia appears to be the main cause of encephalopathy. Hyperammonemia may arise because of increased renal ammonia production due to reduced glutamine synthesis. The condition may also be due to the inhibition of carbamyl phosphate synthetase or the reduction of hepatic ammonia metabolism owing to decreased carnitine availability, which leads to suppression of fatty acid beta-oxidation.

Conclusion. Encephalopathy is a potentially serious consequence of the use of VPA. Physicians should consider this possible cause of changes in mental status in patients treated with VPA. Patients with VPA-induced hyperammonemia may be asymptomatic, may have behavioural changes, or may have marked deteriorations in their level of consciousness.

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- Valproate-induced hyperammonemia as a cause of altered mental status. *Am J Geriatr Psychiatry*. 2002;10(4):476–478.
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